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PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

PCT

Translation

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

Date of mailing
(day/month/year)

Applicant's or agent's file reference

09635

FOR FURTHER ACTION

See paragraph 2 below

International application No.

PCT/JP2004/005456

International filing date (day/month/year)

16.04.2004

Priority date (day/month/year)

18.04.2003

International Patent Classification (IPC) or both national classification and IPC

Applicant

SENJU PHARMACEUTICAL CO. LTD.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/JP

Authorized officer

Facsimile No.

Telephone No.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/JP2004/005456

| Box No. I | Basis of this opinion |
|-----------|--|
| 1. | <p>With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.</p> <p><input type="checkbox"/> This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rule 12.3 and 23.1(b)).</p> |
| 2. | <p>With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:</p> <p>a. type of material</p> <p><input type="checkbox"/> a sequence listing</p> <p><input type="checkbox"/> table(s) related to the sequence listing</p> <p>b. format of material</p> <p><input type="checkbox"/> in written format</p> <p><input type="checkbox"/> in computer readable form</p> <p>c. time of filing/furnishing</p> <p><input type="checkbox"/> contained in the international application as filed.</p> <p><input type="checkbox"/> filed together with the international application in computer readable form.</p> <p><input type="checkbox"/> furnished subsequently to this Authority for the purposes of search.</p> |
| 3. | <p><input type="checkbox"/> In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.</p> |
| 4. | <p>Additional comments:</p> |

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Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 13-16

because:

☒ the said international application, or the said claims Nos. 13-16
relate to the following subject matter which does not require an international preliminary examination (*specify*):

The subject matter of claims 13-16 relates to a method for treatment of the human body by therapy.

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. _____
are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. _____ are so inadequately supported
by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. 13-16

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form

☐ has not been furnished

☐ does not comply with the standard

the computer readable form

☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

☐ See Supplemental Box for further details.

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| Box No. V | Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement | | |
|---|--|-------------|-----|
| 1. Statement | | | |
| Novelty (N) | Claims | <u>1-12</u> | YES |
| | Claims | | NO |
| Inventive step (IS) | Claims | | YES |
| | Claims | <u>1-12</u> | NO |
| Industrial applicability (IA) | Claims | <u>1-12</u> | YES |
| | Claims | | NO |
| 2. Citations and explanations: | | | |
| <u>Claims 1-12</u> | | | |
| <p>Document 1: M. NEGISHI et al., Seikagaku, 2002; 74 (5), 395-8, [Japanese] Document 2: M. NIKOLIC, Int. J. Biochem Cell Biol, 2002, 34(7): 731-45 Document 3: M. LEHMANN et al., J. Neurosci., 1999, 19(17), 7537-47 Document 4: P. DERGHAM et al., J Neurosci, 2002, 22(15), 6570-7 Document 5: US 2002/0119140 A1 Document 6: WO 02/083175 A1 & EP 1378247 A1 Document 7: WO 01/068607 A1 & EP 1270570 A1 Document 8: JP 2003-073357 A</p> <p>As described in documents 1-8, the fact that the formation and expansion of neurite outgrowth is facilitated by inhibition of Rho is confirmed in a plural type of neurons. As a result, studying the effect for corneal nerves using a Rho inhibitor can be easily carried out by a person skilled in the art based on the knowledge obtained from these documents. Making use of the effect that the corneal nerves have on a variety of different diseases could easily be foreseen by a person skilled in the art.</p> | | | |

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Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

The subject matter of claims 1-12 relates to an agent for promoting corneal neural outgrowth formation, an agent for promoting extension of corneal neural axons, an agent for repairing corneal perception and a dry eye therapeutic agent whose active ingredient is a compound defined by the desired characteristics as a "Rho protein inhibitor." The subject matter of claims 1-12 encompasses all compounds which have these properties. However, what is disclosed in the sense of PCT Article 5 is merely an extremely small part of the compound claimed and is not fully supported by the disclosure of the specification in the sense of PCT Article 6.

Furthermore, even after taking into consideration the common general technical knowledge at the time of filing, the "Rho protein inhibitor" cannot specify the scope of the compounds which have these properties; therefore, claims 1-12 lack the requisite clarity of PCT Article 6.